Delavirdine

Brand Name: Rescriptor
Drug Class: Non-nucleoside Reverse Transcriptase Inhibitors

Drug Description

Delavirdine mesylate is a bis(heteroaryl)piperazine (BHAP) derivative nonnucleoside reverse transcriptase inhibitor (NNRTI). [1]

HIV/AIDS-Related Uses

Delavirdine mesylate was approved by the FDA on April 4, 1997, for use in combination with at least two other antiretroviral agents for the treatment of adults with HIV-1 infection. The safety and effectiveness of delavirdine have not been established in neonates and children younger than 16 years of age.[2] [3]

Pharmacology

Delavirdine binds directly to HIV-1 reverse transcriptase (RT) and blocks RNA- and DNA-dependent DNA polymerase activities. Delavirdine does not compete with template, primer, or deoxynucleoside triphosphates. HIV-2 RT and human cellular DNA polymerases are not inhibited by delavirdine. HIV-1 group O, a group of highly divergent strains that are uncommon in North America, may not be inhibited by delavirdine.[4]

Delavirdine is rapidly absorbed following oral administration.[5] The bioavailability of delavirdine 100 mg tablets is increased by approximately 20% when the medication is dissolved in water prior to administration; however, this is not necessarily a preferred method of administration in patients able to swallow oral tablets. Delavirdine 200 mg tablets are not readily dispersed in water and should be swallowed intact.[6] When multiple doses of delavirdine were administered with food, peak plasma concentration (Cmax) was reduced by approximately 25%, but area under the plasma concentration-time curve (AUC) and minimum plasma concentration (Cmin) were not altered.[7]

Delavirdine is distributed predominantly into blood plasma.[8] Delavirdine is approximately 98% bound to plasma proteins, principally albumin. The percentage that is protein bound is constant over delavirdine concentrations of 0.23 to 89.5 mcg/ml.[9] In HIV-1 infected patients whose total daily dose of delavirdine ranged from 600 to 1,200 mg, cerebrospinal fluid concentrations of delavirdine averaged 0.4% of the corresponding plasma delavirdine concentrations; this represents about 20% of the fraction not bound to plasma proteins. Steady-state delavirdine concentrations in the saliva of HIV-1 infected patients and in the semen of healthy volunteers were about 6% and 2%, respectively, of the corresponding plasma delavirdine concentrations collected at the end of a dosing interval.[10]

Delavirdine is in FDA Pregnancy Category C; no adequate and well-controlled studies of delavirdine have been conducted in pregnant women.[11] It is not known whether delavirdine crosses the placenta in humans, but this does occur in laboratory animals. Delavirdine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To monitor maternal-fetal outcomes of pregnant women exposed to delavirdine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263 or at the following web site: http://www.APRegistry.com.[12] It is not known whether delavirdine is distributed into human breast milk; however, it is distributed into milk in rats. Breast-feeding is not recommended for HIV infected mothers because of the potential for HIV transmission to the breast-fed infant.[13]

Delavirdine is extensively converted to several inactive metabolites. It is primarily metabolized by cytochrome P450 3A (CYP3A), but in vitro data suggest that delavirdine may also be metabolized by CYP2D6. Delavirdine reduces the activity of CYP3A, thereby inhibiting its own metabolism. Inhibition of CYP3A by delavirdine is reversible within 1 week after discontinuation of therapy. The major metabolic pathways for delavirdine are N-desalkylation and pyridine hydroxylation.[14] [15]

Delavirdine exhibits nonlinear steady-state elimination pharmacokinetics, with apparent oral

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Pharmacology (cont.)

clearance decreasing by about 22-fold as the total daily dose of delavirdine increases from 60 to 1,200 mg/day.[16] Mean elimination time from plasma is approximately 5.8 hours following treatment with 400 mg three times a day. The apparent half-life increases with dose. The time to peak plasma concentration is approximately 1 hour. The mean steady-state concentration in plasma is approximately 16.1 mcg/ml following doses of 400 mg three times a day. Systemic exposure as measured by the AUC is approximately 82.8 mcg/ml per hour; trough concentration is approximately 6.9 mcg/ml. The median AUC in female patients is 31% higher than in male patients.[17]

In a study of six healthy adults who received multiple doses of delavirdine, approximately 44% of the radiolabeled dose was recovered in feces and approximately 51% of the dose was excreted in urine as metabolites. Less than 5% of the dose was recovered unchanged in urine.[18] The pharmacokinetics of delavirdine in patients with hepatic or renal impairment have not been investigated; however, delavirdine is metabolized primarily by the liver and should be used with caution in patients with impaired hepatic function.[19]

Resistant virus emerges rapidly when delavirdine is used as monotherapy. Acquisition of a single mutation can confer resistance to delavirdine. Genotypic analysis of viral isolates from patients receiving delavirdine and zidovudine revealed that 84% had resistance-associated mutations after 24 weeks of therapy. Mutations occurred predominantly at HIV RT amino acid position 103 but also at positions 181 and 236.[20]

Delavirdine may confer cross resistance to other NNRTIs.[21] Cross resistance between nucleoside reverse transcriptase inhibitors or protease inhibitors is unlikely.[22]

Adverse Events/Toxicity

Rash is the most frequently reported adverse effect of delavirdine. Most cases occur within the first 1 to 3 weeks of therapy; severe rash generally occurs within the first 28 days. The rash is usually diffuse, maculopapular, erythematous, and often pruritic, appearing mainly on the upper body and proximal arms and decreasing on the neck, face, and the rest of the trunk and limbs. In most cases, the rash lasts less than 2 weeks and does not require dose reduction or discontinuation. If delavirdine therapy is interrupted due to rash, most patients are able to resume therapy with the drug after rechallenge.[23]

Severe rash, including rare cases of erythema multiforme and Stevens-Johnson syndrome, has been reported in patients receiving delavirdine. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, and muscle or joint aches should discontinue delavirdine and consult a physician.

Adverse events of moderate to severe intensity reported by at least 5% of patients receiving delavirdine in clinical trials involved the following systems: body as a whole (generalized abdominal pain, asthenia, fatigue, fever, flu syndrome, headache, and localized pain; digestive (diarrhea, nausea, and vomiting); nervous (anxiety, depressive symptoms, and insomnia); and respiratory (bronchitis, cough, pharyngitis, sinusitis, and upper respiratory tract infections.[24]

Postmarketing adverse events not reported in clinical trials have included hepatic failure, hemolytic anemia, rhabdomyolysis, and acute kidney failure. Because these events were observed during clinical practice, their frequency cannot be determined.[25]

Drug and Food Interactions

Delavirdine may be administered with or without food.[26]

Dosage adjustment of delavirdine and/or other drugs may be necessary in patients receiving concomitant therapy with drugs that are extensively metabolized by or induce or inhibit CYP3A, CYP2C9, CYP2D6, and CYP2C19. Delavirdine may inhibit the metabolism of and is predicted to result in clinically important plasma concentration increases in certain amphetamines; anticoagulants (warfarin); anti-infectives (clarithromycin, dapsone,

Drug and Food Interactions (cont.)

and rifabutin); sedative hypnotics (alprazolam, midazolam, triazolam); cardiovascular agents (nifedipine, quinidine); ergot alkaloids and derivatives; GI drugs (cisapride); HMG-CoA reductase inhibitors (atorvastatin, cerivastatin, fluvastatin); immunosuppressive agents (cyclosporine, sirolimus, tacrolimus); methadone; or sildenafil.

Because delavirdine is an inhibitor of CYP3A, concomitant use with an HIV protease inhibitor (PI) may result in increased plasma concentrations of the PI. Delavirdine may inhibit metabolism of indinavir, increasing the Cmax and AUC of indinavir. Although no pharmacokinetic studies have been performed, the possibility exists that delavirdine may increase plasma concentrations of amprenavir and lopinavir. Concomitant use of delavirdine with nelfinavir may result in increased concentration of nelfinavir and decreased concentration of delavirdine and the active nelfinavir metabolite (nelfinavir hydroxy-t-butylamide). Concomitant use of delavirdine with saquinavir may result in increased AUC of saquinavir and decreased AUC of delavirdine. Recent studies indicate that concomitant administration of delavirdine and ritonavir may result in a 70% increase of ritonavir trough concentrations and ritonavir systemic exposure.

Pharmacokinetic studies evaluating concomitant use of delavirdine and other NNRTIs have not been performed.

Doses of delavirdine and buffered preparations of didanosine should be separated by at least 1 hour.[27]

Concurrent administration of delavirdine with aluminum and magnesium oral suspension decreased the AUC for delavirdine by approximately 41%; patients should be advised not to take antacids within 1 hour of taking delavirdine.[28]

Coadministration of St. John's wort or St. John's wort-containing products with NNRTIs, including delavirdine, is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of delavirdine and lead to loss of virologic response and possible resistance to delavirdine and other NNRTIs.[29]

Concurrent use of delavirdine with carbamazepine, phenobarbital, or phenytoin substantially decreases the trough plasma concentration of delavirdine.

Cimetidine, famotidine, nizatidine, and ranitidine increase gastric pH and may reduce absorption of delavirdine; long-term use of these medications with delavirdine is not recommended.

Concurrent administration of delavirdine with clarithromycin increases the AUC for delavirdine by approximately 44%. The AUC for clarithromycin increases by approximately 100%.

Concurrent administration of delavirdine and fluoxetine increases the trough plasma concentration of delavirdine by approximately 50%.

Concurrent administration of delavirdine and ketoconazole increases the trough plasma concentration of delavirdine by approximately 50%.

Concurrent administration of delavirdine with rifabutin or rifampin decreases the AUC for delavirdine by approximately 80% and 96%, respectively, and increases the AUC for rifabutin by at least 100%.[30]

Contraindications

Delavirdine tablets are contraindicated in patients with known hypersensitivity to any of the tablet's ingredients. Coadministration of delavirdine mesylate is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These drugs include ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), neuroleptics (pimozide), sedatives/hypnotics (alprazolam, midazolam, triazolam), and three drugs that are no longer available in the United States (astemizole, terfenadine, and cisapride).[31]

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Clinical Trials

For information on clinical trials that involve Delavirdine, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Delavirdine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[32]

Dosage Form: Tablets containing 100 or 200 mg of delavirdine mesylate.

The recommended dose of delavirdine is 400 mg (four 100 mg or two 200 mg tablets) three times daily.[33]

Storage: Store at controlled room temperature of 20 C to 25 C (68 F to 77 F). Keep container tightly closed. Protect from high humidity.[34]

Chemistry

CAS Name: Piperazine, 1-[3-[(1-methylethyl)amino)-2-pyridinyl]-2-pyridinyl]-4-[[5-[(methylsulfonyl) amino]-1H-indol-2-yl]carbonyl]-, monomethanesulfonate[35]

CAS Number: 147221-93-0[36]

Molecular formula: C22-H28-N6-O3-S.C-H4-O3-S[37]

C49.98%, H5.84%, N15.21%, O17.37%, S11.60%[38]

Molecular weight: 552.68[39]

Melting point: 226-228 C[40]

Physical Description: Odorless white-to-tan crystalline powder.[41]

Solubility: The aqueous solubility of delavirdine free base at 23 C is 2942 mcg/ml at pH 1.0, 295 mcg/ml at pH 2.0, and 0.81 mcg/ml at pH 7.4.[42]

Other Names

U-90152S[43]

DLV[44]

136817-59-9[45]

Delavirdine mesylate[46]

Further Reading

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Manufacturer Information

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Delavirdine

Manufacturer Information (cont.)

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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